

Exhibit A

Lewis Declaration

agonist to enhance a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a); and

- (g) contacting said inverse agonist with a mammal comprising said receptor of step (a) and confirming that said inverse agonist reduces said selected physiological function, or contacting said agonist with a mammal comprising said receptor of step (a) and confirming that said agonist enhances said selected physiological function

wherein said directly identified non-endogenous candidate compound of step (e) was not, prior to such direct identification, indirectly identified as an agonist or antagonist to said receptor.

EXHIBIT A

I, **MICHAEL E. LEWIS, Ph.D.**, do hereby declare as follows:

1. I am currently the President of BioDiligence Partners, Inc., in West Chester, Pennsylvania. I am a co-founder of and Scientific Consultant to Arena Pharmaceuticals, Inc., the owner of the present patent application. I am also the co-founder of several other biopharmaceutical companies, for example, Cephalon, Inc., West Chester, PA and Adolor Corporation, Malvern, PA. In 1973, I received my B.A. in Psychology at George Washington University, Washington, DC; my M.A. in Psychology at Clark University, Worcester, MA in 1975; and my Ph.D. in Psychology at Clark University in 1977. In addition, I have been a journal referee for several journals, including: Biochemical Pharmacology; Brain Research; Endocrine Journal; Experimental Neurology; Molecular and Cellular Neurosciences; Proceedings of the National Academy of Sciences; and Science. I have been involved in several drug discovery development programs including: Myotrophin (IGF-I) Program at Cephalon, Inc.; ACPC Development at Symphony Pharmaceuticals, Inc.; and ADL 2-1294 Development at Adolor Corporation. A copy of my Curriculum Vitae is attached to my declaration as **Appendix A**.

2. As a consultant to Arena, I receive cash payments. I have also received stock from Arena. I have not been compensated by Arena for making this declaration.

3. Through my research activities, I am familiar with G protein-coupled receptors ("GPCRs"), as well as the significance of the expression pattern of a GPCR as it relates to a physiological function within the human body.

4. I am familiar with the procedures and requirements for obtaining a patent. I am the named co-inventor of several issued United States Patents. In this context, I am familiar with the phrase "new matter." I have reviewed and am familiar with Arena's patent application entitled "A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful in the Treatment of Disease," the previous correspondences mailed on November 13, 2000 and March 29, 2000, as well as the underlying correspondence between Arena and the Patent Office. I have reviewed the Office Action dated June 19, 2001.

EXHIBIT A

5. In my opinion, the "Location" and "Correlated Physiological Function" of claims 33 and 39 were established and reported prior to the April 14, 1997 filing date of this patent application. I refer to the following references, which are intended to be exemplary, all available prior to April 14, 1997:

- (a) Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition (1996)
- (b) Harrison's, Principle of Internal Medicine, 13th Edition, (1994)
- (c) Daube, J. et al. Medical Neurosciences, An Approach to Anatomy, Pathology and Physiology by Systems and Level (1978)
- (d) Kandel, E. et al., Essentials of Neural Science and Behavior (1995)
- (e) Kandel, E. et al., Principles of Neural Science, 3rd Edition (1991)
- (e) Isaacson, R. The Limbic System, 2nd Edition (1982).

Appendix B, which is attached to my declaration, is a chart listing the Location and Correlated Physiological Function as set forth in claims 33 and 39, together with the literature citation indicating the relationships set forth in **Appendix B**. For clarity I note: these relationships, in my opinion and based upon the cited references, were established, understood and recognized prior to the filing date of the present patent application.

6. Based upon my research experiences and activities, it is my opinion that the expression location of a receptor in a specific tissue can provide a scientist with the ability to determine a putative functional role of the receptor. This, in my opinion, is evident from the information in **Appendix B**. Furthermore, expression of a receptor in diseased organs can assist one in assessing for clinical relevance of the receptor.

7. Based upon a restriction requirement issued by the Patent Office, Arena has elected number 116 in claims 33 and 39 for further review; this relationship is as follows:

Location:	Correlated Physiological Function:
116. ventromedial hypothalamus	116. food intake

EXHIBIT A

8. I have read the Declaration of Stanley J. Watson (the "Watson Declaration") previously filed with the Response to the Office Action mailed on November 13, 2000¹. In Paragraph 22(a)2(b) of the Watson Declaration, Dr. Watson refers to a GPCR designated by Arena with the code-name 18F. According to the Watson Declaration, 18F is a GPCR localized in several areas of the brain including the hypothalamus, an area of the brain associated with feeding; upon use of the claimed invention applied to this receptor to directly identify a small molecule candidate compound, this compound when administered to laboratory animals "decreased food consumption." In accordance with number 116, a receptor's (*e.g.*, 18F) location (*e.g.*, ventromedial hypothalamus) is correlated with a physiological function (*e.g.*, food intake). Upon identification of the 18F GPCR within the location of 116, *i.e.*, the ventromedial hypothalamus, the correlated physiological function of 116, *i.e.*, food intake, was established. By applying the claimed invention, a candidate compound was directly identified as an inverse agonist that, in this example, when administered to an animal, reduced a physiological function associated with the receptor, *i.e.*, decreased food intake. As is apparent, the directly identified inverse agonist binds to the 18F receptor. I have been informed and I believe that the 18F receptor is a receptor for which the endogenous ligand has not been identified.

9. In my opinion, the claims listing specific Locations and Correlated Physiological Functions are mere delineations of specific relationships that fall within the broad disclosure of the original application, and as I note above, these delineations were understood and publicly available prior to the filing date of this patent application. For example, the following is noted in the application:

"For example, scanning both diseased and normal tissue samples for the presence of a receptor now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand. Since, by definition, the endogenous ligand for an orphan receptor is not known, tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor, for which modulating compounds are now known, with a disease. The DNA sequence of a receptor may be used to

¹ I further note, as is set forth in Paragraph 3 of Dr. Watson's Declaration, that I received post-doctoral training in his laboratory.

EXHIBIT A

make a probe for RT-PCR identification of the expression of the receptor in the tissue samples. The presence of the receptor in a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue strongly can be preferably utilized to identify a correlation with that disease. **Receptors can equally well be localized to regions of organs by this technique. Based upon the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.**" Page 33, line 25 to page 34, line 12 (emphasis supplied).

The location-function relationships of claims 33 and 39 are exemplary, in my opinion, of the broad disclosure provided in the patent application as filed.

10. I have been informed and I believe that utilizing *in situ* hybridization, tissue samples were examined for expression of the GPCR referred to by Arena as 19AL. Upon review of the data, I believe that the data show that the 19AL receptor is expressed in the lateral region of the hypothalamus, which as set forth in number 106 of claims 33 and 39, is correlated to the physiological function of food intake. This physiological function is the same as set forth in number 116, and the regions (lateral region of the hypothalamus and ventromedial hypothalamus) are both areas within the hypothalamus.

11. The phrase "compound efficacy" is defined as follows in the patent application:

"Compound efficacy shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity..." Page 18, lines 3 to 4 of the Specification.

By this definition, the claimed invention does not rely upon the mere binding of a candidate compound to a receptor's endogenous ligand binding site (binding affinity). It is clear that not only must the compound identified by the claimed method bind to the receptor, but in my scientific opinion, more importantly, the compound must inhibit or stimulate the function of the receptor. Based upon my education and work related experiences, in my scientific opinion, the compound efficacy is far more relevant in terms of the activity of the compound on the receptor than measuring the affinity for which the compound binds to a receptor's endogenous ligand binding site. In other words, a compound may have a

EXHIBIT A

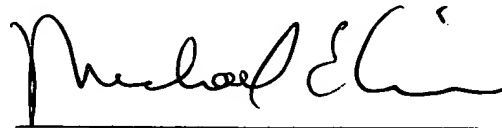
"strong" binding affinity for a receptor but have little or no effect on the function of the receptor, but as defined in the specification, an "inverse agonist" and an "agonist" specifically define for a scientist what functional effect such a compound will have on the receptor. Binding affinity merely defines the ability of a compound to bind to the endogenous ligand binding site of the receptor.

12. To clarify, in my scientific opinion, knowing the binding affinity will not define the functional activity of a compound to a receptor, which is much more significant in identifying candidate compounds.

13. To verify that a directly identified candidate alters the physiological function of the receptor, the claimed method provides for contacting the directly identified candidate compound with a mammal and confirming the alteration of the physiological function. In my scientific opinion, an orphan receptor processed through the claims is less of a "pure" orphan receptor because upon application of the claimed invention, the candidate compound has been directly identified to bind to the receptor and alter a physiological function associated with the receptor. Although by definition the "candidate compound" is not the endogenous ligand, it is my scientific opinion that a candidate compound that is directly identified in accordance with the claims has a real world use because, in accordance with the claims, such a compound will impact a defined physiological function in a mammal.

I further declare that statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 18th day of July, 2001 at West Chester, PA.

A handwritten signature in black ink, appearing to read "Michael E. Lewis", written over a horizontal line.

Michael E. Lewis, Ph.D.